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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/784,528	02/23/2004	Arthur M. Brown	22884/04085	1521

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CALFEE HALTER & GRISWOLD, LLP
800 SUPERIOR AVENUE
SUITE 1400
CLEVELAND, OH 44114

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
12/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,528	BROWN ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-8,10,11,14,15,17,18,24 and 25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-8,10,11,14,15,17,18,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of September 28, 2007, to the non-final action dated March 27, 2007 has been entered. Claims 2, 5, 9, 12, 13, 16 and 19-23 have been cancelled. Claims 1, 3, 4, 6, 10, 11, 14, 15, 17 and 18 have been amended, and claims 24 and 25 newly added.

Accordingly, claims 1, 3, 4, 6-8, 10, 11, 14, 15, 17, 18, 24 and 25 are pending in the Application and currently under examination.

Response to Objection to Drawings & Failure to Comply with Nucleotide and /or Amino Acid Sequence Disclosures 37CFR §1.821-1.825s

Figure 10 was objected to as lacking SEQ ID NOS, in the previous office action dated March 27, 2007. In view of Applicants' submission of a new sequence listing, and amendment to the brief description of the Figure to refer to the protein sequences by appropriate SEQ ID NOS, the previous objection is hereby withdrawn.

Response to Claim Objections

Claims 1-10 were objected to as being incomplete, in the previous office action dated March 27, 2007. In view of Applicant's claim amendments limiting the claimed method to delivery of a nucleic acid encoding human KChAP protein, the previous objection is hereby withdrawn.

New Claim Objections

Claim 3 is newly objected to for the duplication of "in the" in the sixth line of the claim.

Claims 15, 17 and 25 are newly objected to as depending from cancelled claim 12. In the interest of compact prosecution, claims 15, 17 and 25 have been examined as dependent from base claim 11.

Response to Claim Rejections - 35 USC § 112- Second Paragraph

Claims 1, 4 and 19 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the previous office action dated March 27, 2007. Applicants' cancellation of claim 19 renders its rejection moot. Applicants have amended claims 1 and 4 to recite the active steps of delivering and expressing a nucleic acid encoding KChAP protein, thus obviating the ground of rejection. Thus, the rejection of claims 1 and 4 is hereby withdrawn.

Response to Claim Rejections - 35 USC § 112, Written Description

Claims 1-19 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, in the previous office action dated March 27, 2007. Applicants' cancellation of claims 2, 5, 9, 12, 13, 16 and 19 renders their rejection moot. In view of Applicants' amendments to base claims 1 and 4 and 11, deleting language directed to variants and proteins related to KChAP, thus obviating the ground of rejection, the previous rejection of the claims is hereby withdrawn.

Response & New Claim Rejections - 35 USC § 112-Scope of Enablement

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 1-19 stand rejected under 35 U.S.C.§112, first paragraph, because the specification fails to provide an enablement for the full scope of the claimed invention. The rejection set forth on pp. 6-11 of the previous office action dated March 27, 2007 is maintained for claims 1, 3, 4, 6-8, 10, 11, 14, 15, 17 and 18 and further applied to newly added claims 24 and 25, for reasons of record.

Applicants' claim amendments removing language regarding variants of KChAP protein and protein related to KChAP partly address the issues outstanding in the rejection. Applicants argue that the present application provides evidence showing that the claimed methods promote apoptosis in prostate cancer cells, whether the cells are in a culture dish or in an animal tumor. Further arguing that the application also provides evidence for delivering and expressing nucleic acids that encode a KChAP protein into cells of prostate tumors that have been created by injecting prostate carcinoma cells into nude mice, that suppressed growth or reduced the size of

these tumors; thus, producing a meaningful benefit in theses animals. Applicants' arguments have been fully considered, but are not found persuasive.

As set forth in the previous office action, it is not clear by what level an increase in intracellular KChAP protein is sufficient to induce apoptosis, or how the levels of KChAP protein may be increased in the cells without a mechanism facilitating their uptake; as the instant claims continue to embrace administration of any nucleic acid encoding human KChAP to a subject, that would include administration of naked plasmid DNA administered by any route, including systemic administration. The prior art has established that delivery of naked plasmid DNA by systemic administration is marked by low transfection efficiency and expression. Applicants should note that delivery to epithelial carcinoma cells does not preclude systemic administration. While the specification describes the intratumoral injection of Ad/KChAp vector, the instant disclosure is silent on any other vector system or any other method of administration. Thus, it is not clear how administration of a naked plasmid expression vector for example, by a systemic route could deliver sufficient KChAP to the site or tumor and further, avoid non-specific delivery to normal cells, thus causing unwanted apoptosis.

Additional issues include the use of cell lines (as opposed to primary tumor cells) and ectopic and heterotopic transplantation of said cell lines (versus orthotopic transplantation or primary tumor cells) in immunodeficient nude mice, as well as the paradox that enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. These issues are particularly relevant in view of the non-specific delivery of the KChAP protein that may result as a consequence of the routes of delivery encompassed by the instant claims and further bring into question the validity of the claimed methods as a therapeutic.

Applicants argue that the references of Kerbel (Cancer &Metastasis Rev. 17:301-304, 1999), Vieweg et al. (Cancer Investigation, 13(2) 193-201, 1995), Hoffman (Invest. New Drugs 17:343-360, 1999) and Wang (Eur. J. Physiol. 448:274-286;2004), cited by the Examiner in the previous office action, fail to provide an indication that the *in vivo* model used by applicants has not successfully been used and can not successfully be used to identify proteins that enhance apoptosis of tumor cells *in vitro* or *in vivo* AND suppress growth of prostate tumors *in vivo*. Such is not found persuasive, because MPEP 2164.05(a) states: "Specification Must Be Enabling as of the Filing Date". The state of the prior art provides evidence for the degree of predictability in

the art and is related to the amount of direction or guidance needed in the specification as filed to meet the enablement requirement. The state of the prior art is also related to the need for working examples in the specification. The cited prior art references need only address those aspects of Applicants' invention that are unpredictable and call for further undue experimentation on the part of a person of skill in the art.

The determination as to whether any necessary experimentation is undue, is made with respect to analysis of the claims with respect to the *Wands* factors (MPEP 2164.01(a)). As previously set forth, the instant claims have been examined in direct accordance to the factors outlined in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). The *Wands* factors are relevant to the question of whether the instant disclosure is enabling for a person of ordinary skill in the art to make and use the claimed invention without resorting to undue experimentation (MPEP §2164.01). The *Wands* factors considered, included the working examples and the amount of direction or guidance presented in the specification, together with the teachings of the prior art, demonstrated a failure to support an enablement for the full scope of the instantly claimed invention.

The evidence of record as a whole indicates that the heterotopic subcutaneous xenotransplantation of cell lines in an immunodeficient mouse fails to reflect human carcinoma and that systemic delivery and expression of KChAP nucleic acid is unpredictable. In view of the deficiencies in the instant specification, a person of ordinary skill in the art would need to carry out further undue experimentation to determine whether a systemic delivery method using any type of expression vector encoding KChAP in a heterotopic tumor model using cell lines would be effective in inducing apoptosis in human epithelial carcinoma in vivo or treating a subject with prostate cancer. Further, "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The prior art teachings of Kerbel et al., Vieweg et al. and Hoffman et al. were cited to demonstrate that orthotopically transplanted tumors do not necessarily recapitulate the 'encouraging' responses of their ectopically (usually subcutaneous) grown counterparts, and that the animal model exemplified in the instant specification, i.e. subcutaneously-growing human

cell lines in immunodeficient mice, do not sufficiently represent clinical cancer, especially with regard to metastasis and drug sensitivity.

Regarding the reference of Wang (Eur. J. Physiol. 448:274-286; 2004; of record), Applicants argue that KChAP is potassium channel modulatory protein that interacts with and binds to many proteins that are not potassium channels. Thus, the effect of KChAP on tumor growth in a subject may be independent of its effect on potassium efflux; and in the sentences immediately following those quoted in the Office Action, Wang states that "Nonetheless, when used strategically, benefits may be attained. It is tempting to propose that K+ channel blockers could be used in the early stage of carcinogenesis to prevent over-proliferation of tumour cells and K+ channel openers might be employed in the late stage of carcinomas to kill the tumour cells. Thus, Wang et al. does not argue against using elevated levels of KChAP to treat subjects with tumors.

Such is not persuasive, because Wang, states: "K^+ channels favor tumor cell proliferation, therefore, inhibition of K^+ channel function or down-regulation of K^+ channel expression should inhibit tumorigenesis...On the other hand, K^+ channels also promote apoptotic cell death...enhancement of K^+ channel activity can facilitate not only tumor cell apoptosis but also tumor cell proliferation. This apparent paradox confounds the manipulation of K^+ channel function and/or expression as an option for the treatment of cancers." (pp. 281-282 bridging). The foregoing is especially relevant in view of the non-specific delivery of the KChAP protein that may result as a consequence of the routes of delivery encompassed by the instant claims and further questions the validity of the claimed methods as a therapeutic. Applicants have failed to address the issue of non-specific delivery of nucleic acid encoding KChAP.

The instant specification states that KChAP variants increase efflux, cause cell shrinkage and activate caspase 3 to produce PARP cleavage. Applicants' argument that the effect of KChAP on tumor growth in a subject may be independent of its effect on potassium efflux is non sequitur, because the effects of KChAP on K^+ channels cannot be ignored and would necessarily be present upon KChAP expression. Moreover, the proposal by Wang K+ that channel openers might be employed in the late stage of carcinomas to kill the tumour cells is simply an invitation to a person of skill in the art to engage in further experimentation to test a hypothesis, whose outcome is unpredictable and thus constitutes further undue experimentation, especially since a

tumor mass generally contains a heterogeneous population of cells at different stages of cancer progression.

Therefore the previous rejection is maintained for claims 1, 3, 4, 6-8, 10, 11, 14, 15, 17 and 18 and is applied to newly added claims 24 and 25, for reasons of record and the preceding discussion.

Conclusion

Claims 1, 3, 4, 6-8, 10, 11, 14, 15, 17, 18, 24 and 25 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached on 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Fereydoun G. Sajjadi, Ph.D.
Examiner, AU 1633

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633